

Non-linear and scale-invariant analysis of the Heart Rate Variability

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Abstract

Human heart rate fluctuates in a complex and non-stationary manner. Elaborating efficient and adequate tools for the analysis of such signals has been a great challenge for the researchers during last decades. Here, an overview of the main research results in this field is given. The following question are addressed: (a) what are the intrinsic features of the heart rate variability signal; (b) what are the most promising non-linear measures, bearing in mind clinical diagnostic and prognostic applications.

A. INTRODUCTION

The heart rate of healthy subjects fluctuates in a complex manner. These nonstationary and nonlinear fluctuations are related mainly to a nonlinear interaction between competing neuroautonomic inputs: parasympathetic input decreases and sympathetic stimulation increases the heart rate. Meanwhile, heart pathologies may decrease the responsiveness of the heart and lead to a failure to respond to the external stimuli. Evidently, such pathologies lead to an overall reduction of the heart rate variability (HRV). Understanding the diagnostic and prognostic significance of the various measures of HRV has a great importance for the cardiology as a whole, because unlike the invasive methods of diagnostics, the required measurements are low-cost and are harmless for the patients. A particularly important application is the prognostics of the patients with increased risk of sudden cardiac death. While the “linear measures” of HRV are nowadays widely used in clinical practice, the importance of more complicated measures have been hotly disputed in the scientific literature during the recent decades.

The layout of this review is as follows. In the first section, general aspects of the heart rate generation, electro cardiogram (ECG) structure, and data acquisition are discussed. In the second section, we give a brief overview of the “linear era” of the HRV analysis. Section three is devoted to the early studies of the non-linearity of HRV, ie. to the methods based on the reconstructed phase space analysis. Here we also provide the modern view on the applicability of these methods. In section four, we discuss the self-affine and multi-affine aspects of HRV (including the wavelet-transform-based techniques). Section five deals with the phenomenon which can be referred to as “intertwining of low- and high variability periods”. Section six examines the effect of synchronization between heart rate and respiration. Section seven provides a brief conclusion.

B. HEART RATE GENERATION, ECG, AND DATA ACQUISITION

The quasi-periodic contraction of cardiac muscle is governed by the electrical signal, which is generated by the sino-atrial (SA) node — a set of electrically active cells in a small area of the right atrium. The signal spreads through the atrial muscle leading to its contraction. It also spreads into a set of specialized cells - the atrio-ventricular (AV) node. Further

the signal spreads via the His-Purkinje bundle (which is a fractal-like set of electrically conductive fibers) to the myocardial cells causing their contraction. ECG is measured as the electrical potential between different points at the body surface. The activity of the SA node by itself is not reflected on the ECG. The electrical activation of the atrial cells leads to the appearance of the P-wave of the ECG. Q, R, S and T waves (see Fig. 1) are caused by the electrical activity of the ventricular muscle. The heart rate is generally measured as the RR-interval t_{RR} — the time-lag between two subsequent R-pikes (R-pike itself corresponds to the ventricular contraction). For the HRV analysis, only the normal heart activity is taken into account. All the QRS-complexes are labelled as normal or arrhythmic. Note that even for healthy patients, some heartbeats can be arrhythmic. Normal-to-normal interval t_{NN} is defined as the value of t_{RR} for such heartbeats, which have both starting and ending R-pikes labelled as normal (see Fig. 1).

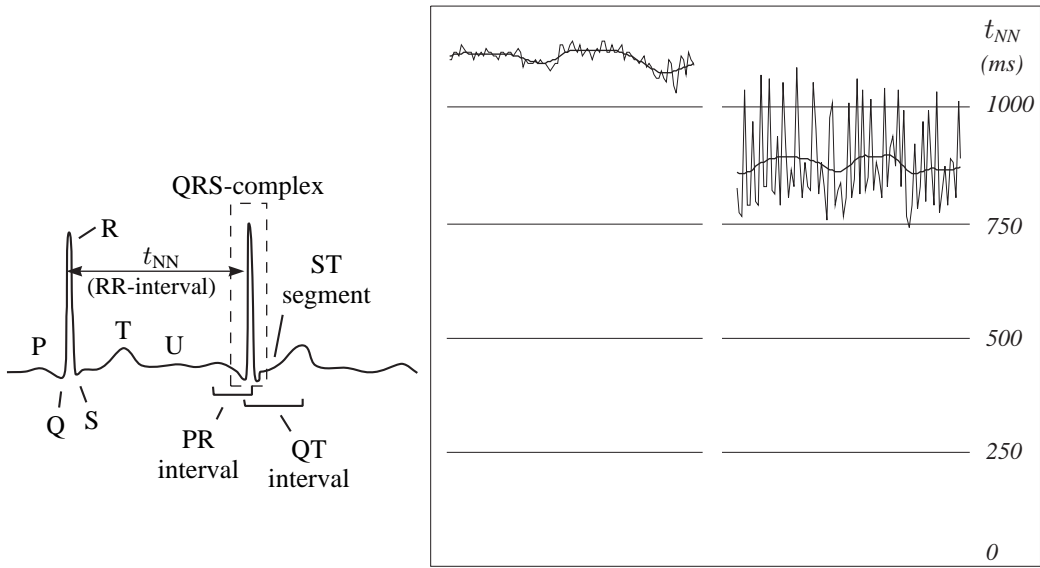


FIG. 1: Left image: normal ECG recording. Image at right: t_{NN} sequences of low- and high variability.

Typically, HRV analysis is based on the 24-hour recordings of the *Holter-monitoring*. Shorter ECG recordings can be used for this purpose, as well; however, in that case it is impossible to observe the long-scale variations and compare the sleep-awake differences in the heart rhythm. Portable apparatus stores the ECG data as the time-dependent voltage $U(t)$ either on a tape or on a PC flash card; the sampling rate is 125 Hz or higher. The data are later analyzed by computer software. Typical commercial software allows visualization of the

ECG recording, automated or semi-automated recognition of arrhythmias and artifacts, and the calculation of the standard “linear” characteristics of the HRV. Most often, a research devoted to the methods of non-linear dynamics is based on plain sequences of NN-intervals, and disregards the details of the continuous ECG recordings. Other aspects of ECG, eg. the clustering of arrhythmic beats [1] and dynamics of QT intervals [2] are also of high clinical importance, but somewhat understudied and will be not discussed here.

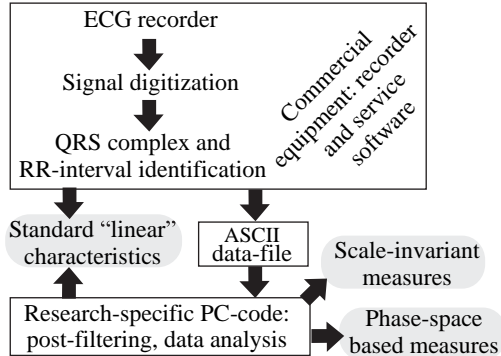


FIG. 2: The analysis of the heart rate variability: the scheme of data acquisition and analysis.

The experimental data serving as the bases of the original research performed by the authors of the review were recorded *(a)* at the Tallinn Nõmme Hospital (children) and *(b)* Tallinn Diagnostic Centre (adult subjects); the scheme of data acquisition is presented in Fig. 2. For the group *(a)*, the recordings of ambulatory Holter-monitoring covered 12 healthy subjects of mean age 11.5 ± 3.3 years, 6 children with clinically documented sinus node disease (mean age 11.5 ± 1.9 years), and 12 subjects with miscellaneous diagnosis. The sampling rate of the ECG was 125Hz. For the group *(b)*, specifics are given in Table 1. These data have been obtained during regular diagnostical examinations of more than 200 patients, the ECG sampling rate has been 180 Hz. The diagnostics and data verification has been made by qualified cardiologist. The data preprocessing included filtering out falsely detected QRS-complexes (artifacts and arrhythmias).

C. LINEAR MEASURES OF HRV

The clinical importance of the heart rate variability (HRV) was first noted in 1965 by Hon and Lee [3]. Since then, the statistical properties of the interbeat interval sequences have attracted the attention of a wide scientific community. An increased risk of post-infarction

	Healthy	IHD	SND	VES	PCI	RR	FSK
No. of patients	103	8	11	16	7	11	6
Mean age	45.5	65.4	50.0	55.9	47.3	55.5	11.7
Std. dev. of age	20.5	11.4	19.3	14.3	11.6	14.4	4.6

TABLE I: Test groups of patients. Abbreviations are as follows: IHD - Ischemic Heart Disease (Stenocardia); SND - Sinus Node Disease; VES - Ventricular Extrasystole; PCI - Post Cardiac Infarction; RR - Blood Pressure Disease; FSK - Functional Disease of Sinus Node.

mortality was associated with the reduced HRV by Wolf et al. in 1977 [4].

Wider attention to the problem has been attained in the early 1980s, when Akselrod et al. introduced the spectral methods for the HRV analysis [5]. The spectral characteristics are generally referred to as “frequency-domain characteristics” and are opposed to the “time domain methods”, which are derived directly from the t_{NN} -sequence. In the late 1980s, the clinical importance of HRV became generally recognized. Several studies confirmed that HRV was a strong and independent predictor of mortality following an acute myocardial infarction [6]–[8]. As a result of this, a breakthrough has been achieved: the “linear” measures of HRV became important tools of clinical practice.

A non-exhaustive list of the parameters which are currently used in medical practice, is as follows: the mean NN interval; the difference between night and day heart rate; longest and shortest NN intervals; the standard deviation of the NN interval (SDNN, typically calculated over 24-hour period); the standard deviation of locally (usually 5 min) averaged NN intervals (SDANN); the mean of the 5-minute standard deviation of the NN interval (averaged over 24 h; SDNN index); the square root of the mean squared differences of successive NN intervals (RMSSD), the percentage of interval differences of successive NN intervals greater than 50 ms (pNN50), the spectral power of high- and low-frequency fluctuations in NN-sequences.

D. RECONSTRUCTED PHASE SPACE

It is widely accepted that the heart rhythm generation in the complex of sinus-node and atrio-ventricular node can be well described by nonlinear dynamical models, where SA node and AV node form a system of nonlinear coupled oscillators [9, 10]. The model has been proven to be viable and predicts several experimentally observed phenomena, such as

Wenkebach and Mobitz type II arrhythmias and bistable behavior [10]. This deterministic non-linear model predicts that the phase trajectories of an healthy heart lie on an attractor of the coupled system of oscillators. Consequently, one should be able to observe well-defined patterns on the Poincarè sections of the phase-space. Note that in the case of physiological data, there is no information, what might be the canonical variables. Therefore, the phase trajectory is reconstructed in time-delay coordinates $U(t), U(t + \tau), \dots, U[t + (D - 1)\tau]$ [or $t_{NN}(n), t(n + 1), \dots, t(n + D - 1)$]. Here D is the so called embedding dimensionality, i.e. the dimensionality of the reconstructed phase-space. It is expected that the real phase trajectory is mapped to the reconstructed trajectory by a smooth transform.

Exactly such a reasoning has lead to the idea that the dynamical characteristics from the theory of non-linear dynamics could be used for the diagnostic purposes. The early studies by Babloyantz et al. [11] gave rise to extensive studies in 1990s [12]–[15]. The experimental observations seemingly confirmed the theoretical expectations. Particularly, the correlation dimension of the continuous ECG recording (i.e. the recorded voltage as a function of time) has been reported to be between 3.6 and 5.2. The conclusion has been that the dynamics of the heart of healthy persons is less regular than that of persons with severe cardiac pathologies. Correspondingly, the correlation dimension has been often thought to be a measure for the healthiness of the heart. The other tools of the analysis of non-linear dynamical systems (such as Lyapunov exponents; Kolmogorov, Shannon, pattern, and approximate entropies; etc) have been exploited in an equal extent.

The correlation dimension of a data sequence is typically calculated according to the Grassberger-Procaccia algorithm [16]. In a reconstructed phase space of dimensionality D , the correlation sum $C = \sum_{i,j} \theta(r - |r_i - r_j|)$ is calculated as a function of the radius r ; it is expected to behave as a power-law $C \propto r^{\nu(D)}$. Here r_i denotes the D -dimensional radius-vector of the i -th data-point, and $\theta(r)$ stands for the Heaviside function. The correlation dimension d_c is found as the limit of ν at large values of D (in fact, it is expected that for $D > d_c$, the exponent ν is independent of D , and in that case $\nu = d_c$).

However, there are various arguments leading us to the conclusion that the formally calculated correlation dimension of a heart rhythm does not correspond to the dimensionality of an intrinsic attractor; similarly, the formally calculated Lyapunov exponents, entropies etc. do not describe the respective aspects of underlying non-linear dynamics. *First*, it has been pointed out that physiological time-series are typically non-stationary and noisy,

and therefore, the correlation dimension cannot be calculated reliably [17, 18, 19]; this fact is nowadays widely accepted. In the case of human heart, the “noise” comes from the autonomous nervous system in the form of inputs regulating the heart rate (cf. [20, 21, 22]): from the viewpoint of underlying nonlinear deterministic system, these effectively non-deterministic signals perform the role of high level noise. It should be also noted that some inputs of the autonomous nervous system may lead to quasi-periodic signals — an easy source of false detection of low-dimensional chaos and apparent patterns in simple time delay maps, see Fig. 3–4. Thus, respiration gives rise to the signal of typical period of 4s; the effect is most pronounced when the patient is at rest, and is stronger for young persons. *Second*, it has been emphasized that a reasonable fitting of a correlation sum to a power law does not necessarily mean that the obtained exponent is the correlation dimension of the underlying dynamical system; instead, thorough non-automatable verification procedure has to be done [23]. *Third*, the length of the data sequences is often inadequate for reliable calculation of high values of the correlation dimension $d_c \gtrsim 6$, cf. [15, 23].

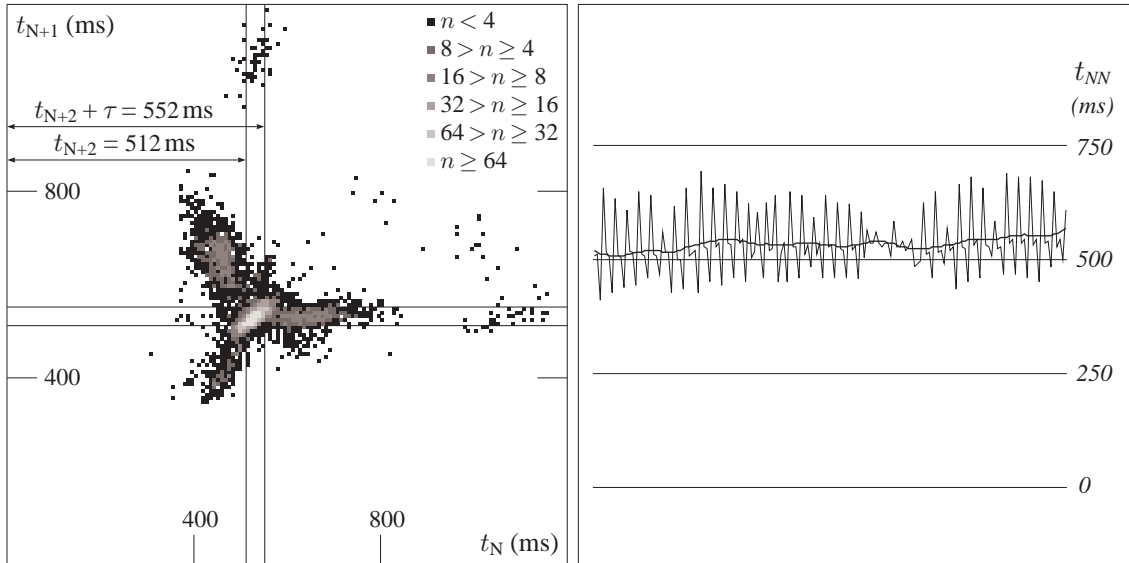


FIG. 3: A cross-section of the 3-dimensional reconstructed phase space for a patient with pronounced 4:1 mode-locking (see also Section G); around the central cloud of points, three major satellite-clouds can be seen; these satellite-clouds correspond to the sequence of interbeat intervals, shown on the right-hand plot. The observed oscillations with period 4 can be attributed to the modulation of the heart rate by respiration.

The above discussed research results can be summarized as follows: (a) the correlation

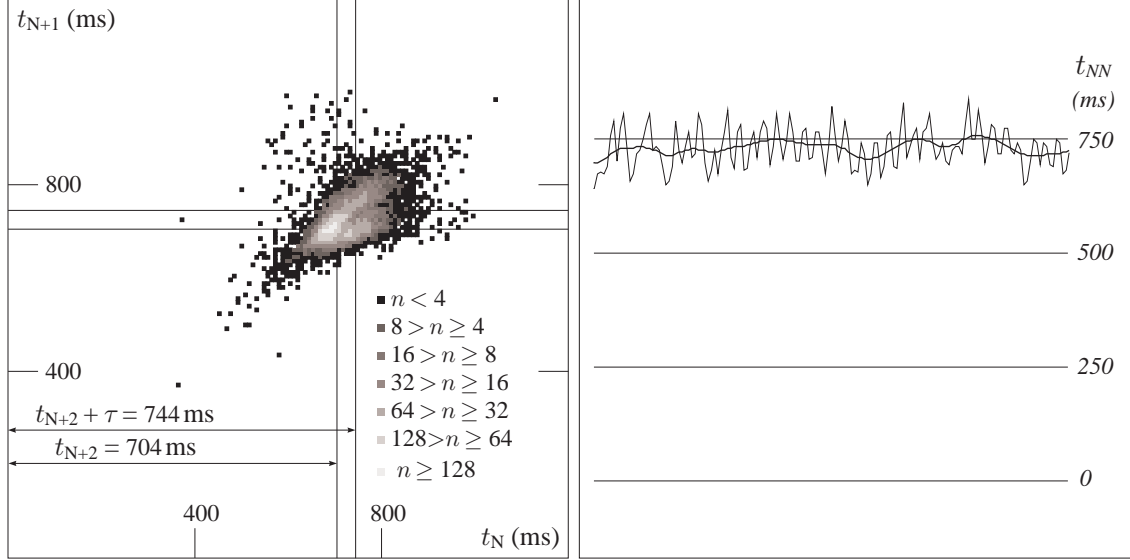


FIG. 4: The same as in Figure 3. Mode-locking (4:1 and 5:1) is weaker, but the heart rate modulation by the respiration is significant. One can distinguish two branches of the central cloud, which are caused by the respiratory modulation.

sums of human heart rate follow typically a scaling law; *(b)* in most cases, the scaling exponents are not the correlation dimensions. This leads us to a natural question: what is the physical meaning of these formally calculated exponents? Our answer to this question is based on simple observations, valid for healthy patients: *(a)* the long-time variability of the inter-beat intervals is typically much higher than the variability on the time scale of few heart beats; *(b)* for those periods, when the mean heart rate is high (when the subject is performing physical exercise) the heart rate variability is low; *(c)* the heart rate is controlled by effectively random non-deterministic inputs arriving from the autonomous nervous system. As a consequence, in time delay coordinates, an HRV time-series generates a baseball bat-shaped cloud of points. Although the theoretical value of the correlation dimension of such a cloud is infinite, the finite resolution of the recording apparatus, finite length of the time-series, and the linear structure of the cloud result in a smaller value. This is evident for a very narrow “bat”, which is efficiently one-dimensional.

Our conjecture passes also a quantitative test: the correlation sum of surrogate datasets constructed using Gaussian random data-series and mimicking the features *(a)*–*(c)* (see Fig. 5) scales almost identically to that of clinical HRV data, see Fig. 6 and Ref. [24].

To conclude, the reconstructed-phase-space-based measures fail in describing a determin-

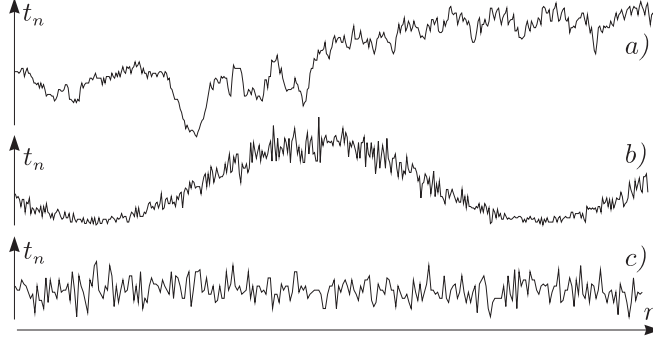


FIG. 5: Time series for real HRV data (a), surrogate data (b), and Gaussian noise (c); the beat interval t_n is plotted versus the beat number n .

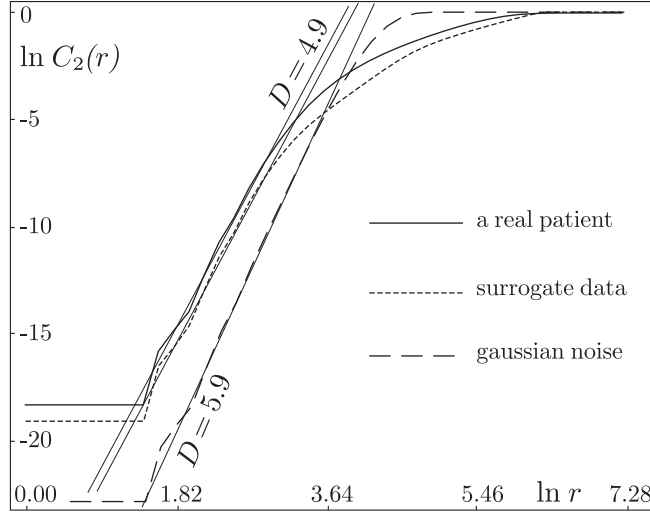


FIG. 6: The correlation sum $C_2(r)$ (as a function of the radius r) of surrogate data scales almost identically to the real clinical data.

istic chaos inside the heart, because the deterministic dynamics is suppressed by essentially intermittent signals arriving from the autonomous nervous system and regulating the heart rhythm. However, some fine-tuned measures (eg. various entropies, cf. [25]) can be useful in describing the level of short-time variability of the heart rhythm, and complement the linear quantity pNN50 (which also measures the high-frequency component of HRV).

E. SCALE-INDEPENDENT MEASURES.

Recent studies have shown that scale-invariant characteristics can be successfully applied to the analysis of the heart rate variability [26]–[29]. However, this conclusion has been

disputed, and certain scale-dependent measures (particularly, the amplitude of the wavelet spectra at specific time-scale) have been claimed to provide better results [30]. The scale-independent methods have been believed to be more universal, subject-independent, and to reflect directly the dynamics of the underlying system, unlike the scale-dependent methods which may reflect characteristics specific to the subject and/or to the method of analysis [29]. Opposing argument has been that certain heart disorders affect the heart rate variability at a specific scale or range of scales; owing to this circumstance, at the properly chosen time-scale, scale-dependent measures may provide a useful information [30].

The simplest relevant scale-independent measure is the Hurst exponent H , which has been introduced to describe statistically self-affine random functions $f(r)$ of one or more variables [31]. Such a function is referred to as *fractional Brownian function* and satisfies the scaling law

$$\langle [f(r_1) - f(r_2)]^2 \rangle \propto |r_1 - r_2|^{2H}.$$

Note that $H = 1/2$ is a special case of ordinary Brownian function — the increments of the function are delta-correlated, and $f(r)$ can be thought to be the displacement of a Brownian particle as a function of time r . Therefore, in the case of $H < 1/2$, there is a negative *long-range correlation* between the increments of the function. Analogously, $H > 1/2$ corresponds to a positive correlation. Note that the early scale-invariant studies of HRV were based on power spectra [32, 33], an aspect closely related to the scaling exponent H .

Many phenomena in nature exhibit this kind of scale-invariance, and lead to fractional Brownian time-series [31]. The same is true for the heart rate variability: after filtering out short-scale components with $\tau < 30$ s (corresponding to the respiratory rhythm, to the blood-pressure oscillations, and to the pathological Cheyne-Stokes respiration), the fluctuation function $F(n)$, defined as

$$F(\nu) = \langle |t_n - t_{n+\nu}| \rangle \quad (1)$$

revealed a good scaling behavior $F(\nu) \propto \nu^H$ [26]. While for healthy patients, the increments of the heart rhythm were found to be significantly anticorrelated resulting in $H < 1/2$, the heart rhythm of the patients with dilated cardiomyopathy was essentially Brownian with $H \approx 1/2$ [26]. In the case of our patient groups, there was no significant correlation between the diagnosis and the Hurst exponent, and there were many healthy subjects with $H \approx 1/2$, see Fig. 7. Finally, various techniques, such as detrended fluctuation analysis [27], detrended

time series analysis [35], and wavelet amplitude analysis [34] have been proposed to fine-tune the Hurst-exponent-based approach.

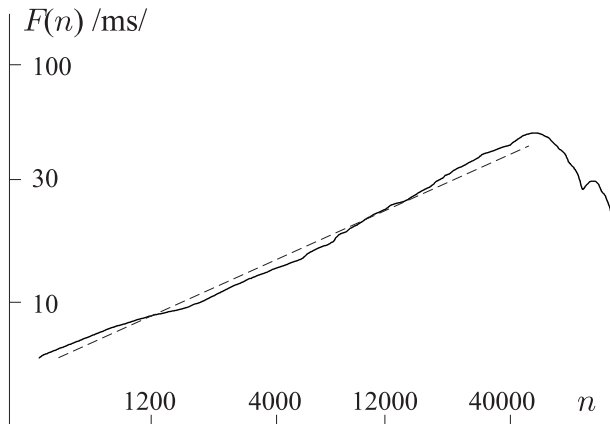


FIG. 7: The fluctuation function $F(\nu)$ is plotted versus the time lag ν . Almost straight line indicates a good scaling behavior $F(\nu) \propto \nu^H$ (here with $H = 0.50$).

Complex non-stationary time-series cannot be described by a single scaling exponent H . Indeed, simple scaling behavior is expected if there is a Gaussian distribution of increments. However, even in the case of Gaussian functions, the scaling exponent is not necessarily constant over the whole range of scales. Instead, it can be a slow (eg. logarithmic) function of the scale, so that other descriptions (such as stretched exponentials) may be required. Physiological time-series are typically non-Gaussian. For such functions, scale-invariance can be very complicated. A non-exhaustive way to describe such behavior is to calculate the multifractal spectrum of Hurst exponents [43]. Therefore, it is not surprising that the human heart rate signal was found to obey a multi-affine structure [28, 29].

Qualitatively, a multifractal time-series behaves as follows. If the whole time-series is divided into short segments, each segment can be characterized by its own Hurst exponent h (referred to as the Lipschitz-Hölder exponent). Then, the distribution of segments of fixed values of h is self-similar, and is described by a fractal dimension $f(h)$. Technically, the spectrum $f(h)$ can be calculated by the means of wavelet transform, cf. [29]. This scheme includes the calculation of the scaling exponents $\tau(q)$ (referred to as the mass exponents), which describe, how the q -th moment of the wavelet transform amplitude scales with the wavelet width. The scaling exponents $\tau(2)$ and $\tau(5)$ have been found to have a significant prognostic value (for the post-infarction prognosis) [29]. The wavelet transform amplitudes,

calculated for a specific wavelet width (≈ 5 min) have been claimed to be of even higher prognostic value [30]. However, independent studies have shown that the scale-invariant measures seem to be superior tools [36]. It should be also noted that the wavelet transform amplitude at a fixed time-scale is closely related to the linear measure SDANN. Substituting the robust standard deviation by a wavelet transform amplitude is a technical fine-tuning which cannot be expected to result in a qualitatively new information.

The multifractal structure of the heart rate signal has several consequences. Thus, the q -th order structure function (a concept borrowed from the theory of the fully-developed turbulence) of the heart rate interval has a scaling behavior, with the scaling exponent $\zeta(q)$ being a function of q [37]. Note that this spectrum of exponents is very closely related to the above-mentioned $\tau(q)$ spectrum (both describing the same physical phenomenon, differences being of a technical kind). However, the wavelet-transform-based technique makes a more complete utilization of the underlying data and therefore, $\tau(q)$ spectrum can be expected to yield somewhat superior prognostic and/or diagnostic results.

Another aspect related to the multifractal nature of the heart rhythm, is the multiscale entropy (MSE) [38]. While the single-scale entropies (approximate entropy, Shannon entropy) are related to the short-time dynamics of the heart rhythm and to the probability distribution function of points in the reconstructed phase space, the multiscale entropy extends these concepts to longer time-scales. MSE is not directly reducible to the multifractal spectra $f(h)$ [or $\tau(q)$]; however, both techniques address the question of how wide is the range of dynamics for the mean heart rate (averaged over a time T), depending on the time-scale T . The clinical usefulness of the MSE is still unclear (apart from the fact that it has been claimed to distinguish between healthy subjects and patients with congestive heart failure [38])

F. INTERMITTENCY OF THE HRV

Multifractal spectrum addresses only one aspect of the non-Gaussianity of the time-series increments by revealing the possible range of scaling laws for the long-range [at time-scale of many ($\gg 1$) heartbeat intervals] dynamics of mean heart rhythm. However, the short-time variability of heart rhythm is also fluctuating in a complex manner. It has been pointed out that the NN-sequences of healthy subjects consist of intertwined high- and low-

variability periods [12]. This conclusion can be easily verified by a simple visual observation of the NN-sequences, see Fig. 8. The quantitative analysis of such a behavior is based on the distribution law of the low-variability periods [39, 40], which will be discussed below. Another aspect of such an intertwining is the clustering of the periods of similar mean heart rate: the heart rate signal can be divided into segments of different mean heart rate, with distinct boundaries between these segments; there is a power-law segment-length distribution of the segments [41].

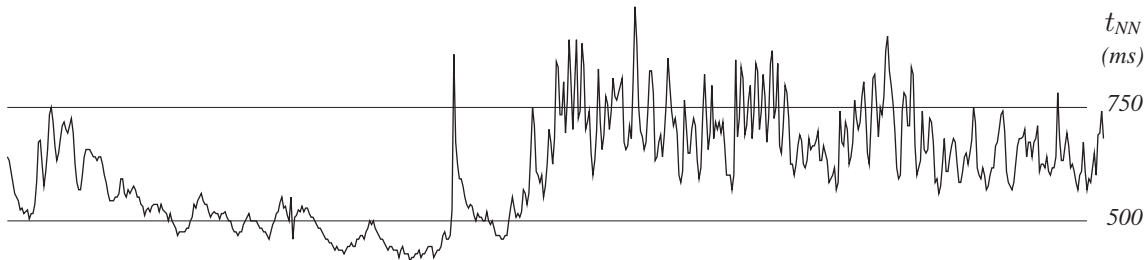


FIG. 8: For healthy patients, the high- and low-variability periods of the heart rhythm are intertwined.

In order to analyze quantitatively the intertwining of high- and low-variability periods, we have studied distribution of low-variability periods and showed that typically, it follows a multi-scaling Zipf's law. Originally, the Zipf's law has been formulated by G. K. Zipf for the frequency of words in natural languages [42]. For a given language (e.g. English), the frequency (the number of occurrences divided by the total number of words) of each word is calculated on the bases of a large set of texts. The ranks are determined by arranging the words according to their frequency f : the most frequent word obtains rank $r = 1$, the second frequent — $r = 2$ etc. It turns out that for a wide range of ranks (starting with $r = 1$), there is a power law $p(r) \propto r^{-\alpha}$, where $\alpha \approx 1$. This law is universal, it holds for all the natural languages and for a wide variety of texts [42]. Furthermore, similar scaling laws describe the rank-distribution of many other classes of objects, as well. Thus, when cities are arranged according to their population s , the population of a city $s \propto r^{-\alpha}$, with $\alpha \approx 1$ [42]. Another example is the income-rank relationship for companies; here we have again $\alpha \approx 1$ [42]. In the most general form, the law can be formulated as $p \propto (r + r_0)^{-\alpha}$, and α is not necessarily close to unity [43]. This more general form of the law can be applied to the distribution of scientists according to their citation index, to the distribution of internet

sites according to the number of visitors etc.

The Zipf's law is characteristic to such dynamical systems at statistical equilibrium, which satisfy the following conditions: *(a)* the system consists of elements of different size; *(b)* the element size has upper and lower bounds; *(c)* there is no intermediate intrinsic size for the elements. The human heart rate, when divided into the low-variability periods, satisfies all these requirements. The duration τ of these periods varies in a wide range of scales, from few to several hundreds of heart beats. Thus, one can expect that the rank-length distribution $r(\tau)$ follows the Zipf's law,

$$r \propto \tau^{-\gamma}. \quad (2)$$

First we have to define the local heart rate variability as the deviation of the heart rate from the local average,

$$\delta(n) = [t_{NN}(n) - \langle t_{nn}(n) \rangle] / \langle t_{nn}(n) \rangle;$$

the local average is calculated using a narrow (≈ 5 -second-wide) Gaussian weight-function. Then, the low-variability regions are defined as consecutive sequences of intervals with $|\delta(n)| < \delta_0$; the length τ of such a region is measured as the number of beats in the sequence. Further, all the low-variability regions are numbered (to identify them later), and arranged according to their length; regions of equal length are ordered randomly. In such a way, the longest observed region obtains rank $r = 1$, second longest — $r = 2$, etc. Typically, the length-rank relationship reveals multiscaling properties, i.e. within a certain range of scales, the scaling law (2) is observed, the scaling exponent γ being a (non-constant) function of the threshold level, $\gamma = \gamma(\delta_0)$; see Fig. 9.

It is not surprising that the scaling behavior is not perfect. Indeed, the heart rhythm is a non-stationary signal affected by the non-reproducible daily activities of the subjects. The non-stationary pattern of these activities, together with their time-scales, is directly reflected in the rank-length law. This distribution law can also have a fingerprint of the characteristic time-scale (10 to 20 seconds) of the blood pressure oscillations (which modulate the level of HRV, cf. [44]). It should be emphasized that the problem of the non-reproducible daily activities affects also the reliability of the other scale-invariant measures and is probably the main obstacle preventing the clinical application of the seemingly extremely efficient diagnostic and prognostic techniques. Finally, there is a generic reason why the Zipf's law is non-perfect at small rank numbers: while the Zipf's law is a statistical law, each rank-

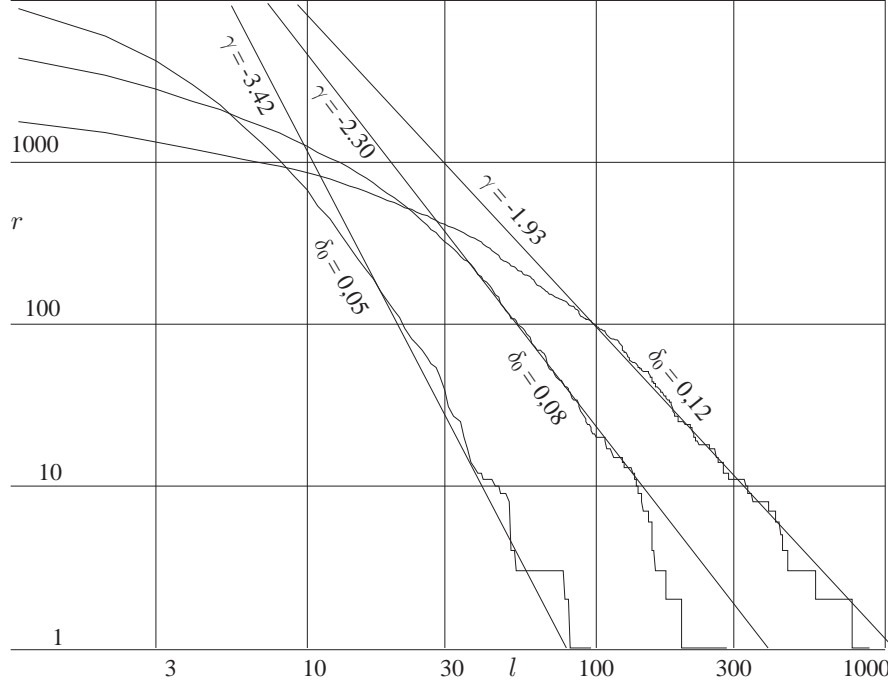


FIG. 9: Multi-scaling behavior: the rank of low-variability intervals is plotted against the length of the intervals. The scaling exponent γ depends on the threshold value δ_0 .

length curve is based only on a single measurement. In particular, there is only one longest low-variability period (likewise, only one most-frequent word), the length of which is just as long as it happens to be, there is no averaging whatsoever. For large ranks, the relative statistical uncertainty can be estimated as $1/\sqrt{r}$.

The distribution function of the low-variability periods as a whole contains a significant amount of diagnostically valuable information, which is not covered by any other (linear or nonlinear) measure of HRV. The most part of this information seems to be reflected (according to the Student test analysis using the test groups of Table 1) by the parameters r_{100} (the rank of the interval with $\tau = 100$), r_{\max} (the maximal observed rank), and τ_{end} (the scale at which the scaling law breaks; for a precise definition, see Ref. [40]). These measures allow a clear distinction between the healthy subjects and the IHD, VES, and PCI groups [40], see also Table 2.

p (%)	Healthy	IHD	SND	VES	PCI	RR	FSK
Healthy	$\begin{matrix} B & A \end{matrix}$	0.06	17.21	0.02	0.07	1.59	1.55
IHD	0.36		2.85	96.79	97.62	21.93	20.05
SND	2.99	59.10		2.10	3.04	25.77	25.57
VES	0.08	91.60	63.79		94.18	17.59	16.20
PCI	25.27	21.61	46.37	22.89		22.50	20.62
RR	0.14	73.57	77.69	80.49	28.90		98.20
FSK	46.48	5.20	8.72	5.52	20.06	6.45	

TABLE II: p -values of the Student test. Data in the topmost triangular region (with label A) are calculated using the parameter $\ln \tau_{\text{end}}$. Triangular region B corresponds to the parameter $\ln r_{\text{max}}$. Since multiple tests were carried out, modified Bonferroni correction [45] has to be applied. Gray background highlights the tests with the adjusted significance $p' < 3\%$. The control parameter value $\delta_0 = 0.05$ has been used.

G. MODE LOCKING BETWEEN HEART RHYTHM AND RESPIRATION

As mentioned above, respiration affects (modulates) the heart rhythm. This effect is mediated by the blood pressure, and the effect known as baroreflex (heart rhythm depends on the blood pressure). The heart is most responsive with respect to the signals of the autonomous nervous system when the heart rate is slow, i.e. when the patient is at rest. In that case, the heart rate variability is driven by weaker signals, like the signals induced by respiration, which (due to their quasi-periodic nature) may lead to a mode-locking. In the case of mode-locking, the heart rate is automatically slightly adjusted so that the respiration and heart beat periods relate to each other as (small) integers. As a result, the decorrelation time between the heart rhythm and respiration can be very long. This is the effect which is in most cases the cause of the patterns (isolated clouds of points) observable in the reconstructed phase space (see Fig. 3).

The mode-locking has been studied using bivariate data (simultaneous ECG and respiration data) and the technique called cardiorespiratory synchrogram [44]. Also, a univariate data analysis method using the angle-of-returntime map has been elaborated [46]. In that case, the data-set is used to reconstruct the phase of forcing (breathing) and the phase of oscillator (heart). These phases are plotted versus each other; in the case of mode-locking, disjoint clouds of points will appear.

Recently, we have developed an independent, intuitive and easy to use method of mode-

locking detection from univariate data (RR-interval sequence), which is based on analysis of the fluctuation function $F(\nu)$, defined by Eq. 1 [24]. The fluctuation function of the patients with mode-locking revealed a presence of an oscillatory component, see Fig. 10b. By dividing the entire 24-hour HRV record into one-hour intervals, and calculating the amplitude of the oscillatory component (via a wavelet transform) of the fluctuation function for each interval, we were able to locate the periods responsible for the satellite clouds in the reconstructed phase space. These were always the periods before falling asleep, around 10 or 11 pm, characterized by a low heart rate and a high respiration-driven short-time variability. The phase between the heart rate and respiration is locked during tens of seconds, confirming the observations of Kurths et al. [44]. Thus, in a certain sense, the heart and respiratory complex act as a system of coupled oscillators. Finally we note that a specific feature of the patients with strong mode-locking was the presence of well-defined “satellite clouds” in time-delay map (see Fig. 3). Therefore, the time-delay map can be also used to detect mode-locking; however, this method is non-quantitative, less sensitive than the fluctuation-function-based technique, and does not give a hint, which mode-locking modes are observed. The presence of a natural quantitative measure [the wavelet transform amplitudes] is also the main advantage of our approach over the alternative method.

As compared with the alternative techniques, our method of mode-locking detection is very simple and does not require synchronous respiration rhythm recording (unlike the thorough method [44]), and can be conveniently used to find relatively short ($\gtrsim 10$ min) locking periods from a 24-hour recording. Besides, it provides a natural measure to quantify the degree of mode-locking (unlike the method of using the angle-of-returntime map [46]).

H. CONCLUSIONS

Below is an attempt to classify the measures of heart rate variability.

1. “linear” methods — based on standard statistical measures and on the Fourier analysis.

These are the only methods, which are widely used in clinical practice.

2. “nonlinear” methods:

- (a) scale-invariant methods:

- i. single-scaling analysis (calculation of the Hurst exponent H);

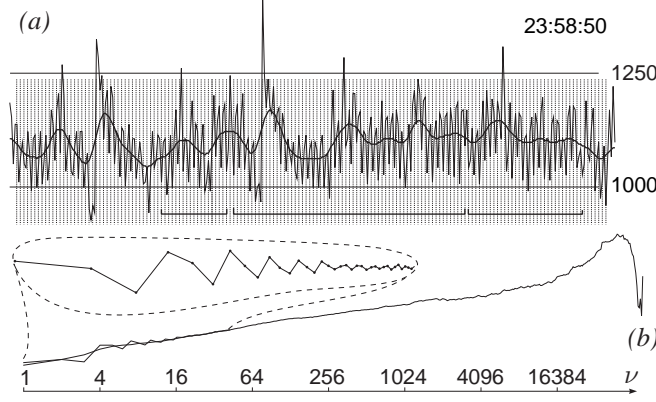


FIG. 10: Patient with 3:1 mode locking between heart rate and respiration: (a) heart beat intervals (in milliseconds) plotted versus the beat number. Heart rate has a pronounced oscillatory component; vertical lines mark the period of three heart beats, horizontal lines indicate the sequences with coherent phase. (b) Fluctuation function (arbitrary units) is plotted versus the time lag ν (in heart beats); the oscillating component is magnified.

- ii. multi-scaling analysis — calculation of the exponent spectra [Lipschitz-Hölder spectrum $f(h)$, mass exponents $\tau(q)$, or structure function exponent spectrum $\zeta(q)$]; these seem to be the most promising measures, at least for prognostic purposes;
 - iii. calculation of the multi-scale entropy;
 - iv. analysis of the HRV-data segments with similar mean heart rate;
 - v. analysis of the distribution law of low-variability periods (performs well in diagnostic tests, there are no prognostic tests yet);
- (b) scale-dependant methods:
- i. performing a phase-space analysis (entropy-based measures, correlation dimension, Lyapunov exponents etc);
 - ii. calculating wavelet spectra at specific time-scales;
 - iii. heart rhythm and respiration mode-locking analysis.

Human heart rate fluctuates in a complex and non-stationary manner. Elaborating efficient and adequate tools for the analysis of such signals has been a great challenge for the researchers during last decades. The above given long list of nonlinear techniques proves that the research has been successful, various important features of such time-series have

revealed. However, there is no consensus of which methods are most efficient from the point of view of clinical applications. On the one hand, this is caused by the high non-stationarity and irreproducibility of these time-series: the complex measures of HRV depend not only on the healthiness of the heart, but also on the daily habits of the subject [47] and on the random events of the recording day. On the other hand, dialogue between physicists and doctors seems to be inefficient: physicists publish research results based on small test groups; doctors are waiting for follow-up studies using extended and homogeneous test groups, but there seems to be no-one who has both necessary resources (funding, mathematical education, access to clinical data-bases), and motivation of doing such analysis.

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